Decreased Synthesis of Brain-derived Neurotrophic Factors in Vascular Endothelial Cells of Clinically Depressed Patients: Implications for Depression Pathogenesis and Treatment

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Abstract

Major depressive disorder (MDD), although one of the most common psychiatric illnesses, has an unknown etiology. Decreased levels of brain-derived neurotrophic factor (BDNF) have been implicated in the pathogenesis of MDD. However, post-mortem studies have not always shown decreased BDNF levels in MDD patients. In contrast, many clinical studies have consistently demonstrated that serum BDNF levels were decreased in MDD patients, and that antidepressant treatment reversed this deficit. Serum BDNF is synthesized primarily in vascular endothelial cells and stored in platelets. Antidepressant treatments and exercise, which have been shown to protect vascular endothelium and increase blood BDNF levels, can alleviate depression. I hypothesize that low serum BDNF is a cause of low brain BDNF, and not a consequence of it, and thus that low serum BDNF is a cause of major depression. Low serum BDNF levels in depressed patients may be the result of decreased BDNF synthesis in vascular endothelial cells in response to stress. Attempts to confirm the association between decreased BDNF synthesis in vascular endothelium and MDD pathogenesis may lead to the development of novel approaches for the prevention and treatment of this common disorder.

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Introduction

Major depressive disorder (MDD) is a common mental disease. Although the causes of MDD are unknown, evidence suggests that brain-derived neurotrophic factor (BDNF), a member of the neurotrophic family that is known to regulate neuronal plasticity, may play a pivotal role in the pathophysiology of major depression, and that agents that can increase BDNF pathway signaling may represent a potential therapeutic approach for this disease [1, 2]. For example, animal studies have shown that decreased hippocampal BDNF expression resulting from environmental stressors can be counteracted by antidepressants [3, 4]. When BDNF was directly administered to stressed animals, it produced an antidepressant-like effect by antagonizing learned-helpless behaviors [5]. However, not all animal studies found that stress reduced hippocampal BDNF mRNA or protein expression [6, 7].

Few post-mortem studies have attempted to address the role of BDNF in MDD pathogenesis, and the existing data do not provide strong correlative evidence. In 2001, Chen et al demonstrated higher BDNF levels in the hippocampal regions of depressed patients treated with antidepressant medication at the time of death than was observed in untreated controls [8]. However, there was no association of MDD diagnosis and BDNF levels in any of the hippocampal regions. Dunham et al found decreased BDNF levels in all layers of the right, but not the left, hippocampus of MDD patients, compared with non-psychiatric controls [9]. In another post-mortem study, BDNF mRNA expression in the midbrain was 3.36 times lower in male suicide victims with major depression, but 5.27 times higher in female victims, compared with gender-matched controls [10]. These

studies suggested that BDNF mRNA and/or protein levels may not be reduced in MDD patients.

Serum BDNF and Depression

The most consistent finding of altered BDNF expression in MDD comes from the clinical study of blood BDNF levels. In 2002, Karege et al first observed that serum BDNF levels were significantly lower in MDD patients than in controls, and that depression severity was the primary contributor to the negative correlation [11]. These findings were replicated by Shimizu et al in a study of antidepressant-naive MDD patients, in which reduced serum BDNF levels returned to basal levels following antidepressant treatment [12]. The finding of decreased serum BDNF levels in MDD patients has been replicated in many subsequent studies, and a meta-analysis of 11 studies revealed strong evidence that BDNF levels were lower in MDD patients, compared with control patients ($P < 6.8 \times 10^{-8}$) [13]. Thus, low serum BDNF may have a direct impact on depression pathogenesis. Alternatively, low serum BDNF may be a peripheral marker for MDD, but the mechanisms by which serum BDNF levels may be reduced in MDD are unclear.

Hypothesis

Serum BDNF is a significant source of brain BDNF, and is reduced in major depression. Treatments that increase serum BDNF, regardless of whether they affect brain BDNF levels, will be effective in treating depression. This will be true whether the treatment directly induces BDNF production (like antidepressants) or indirectly improves endothelial health or reduces endothelial stress (like exercise). I propose that the low serum BDNF levels in MDD patients is the result of reduced BDNF synthesis in vascular endothelial cells, which contributes to MDD pathogenesis by modulating BDNF levels in the brain, based on the following evidence.

First, although BDNF is highly concentrated in the central nervous system (CNS), it is also present in human and rat plasma, and is much more concentrated in the serum [14]. Blood BDNF is stored primarily in the platelets, from which it can be released into the blood by agonist stimulation [15]. However, no BDNF mRNA was detected in northern blot examinations of platelets and megakaryocytes, the progenitor cells for platelets [15]. This evidence indicates that BDNF mRNA and protein expression does not occur in platelets or megakaryocytes, and that BDNF is acquired from other sources through blood circulation. Nakahashi et al demonstrated that

BDNF mRNA and protein were detected in cultured cells and in the culture medium of human umbilical vein endothelial cells, suggesting that vascular endothelial cells may contribute to circulating BDNF [16]. Furthermore, cerebrovascular endothelial cells have also been shown to be a potential source of bioactive BDNF [17].

BDNF is produced from the pro-BDNF precursor that is proteolytically cleaved to yield the mature protein. Mature BDNF is a 14 kDa protein that may penetrate the blood-brain barrier poorly. However, animal studies demonstrated that intravenously injected BDNF can cross the blood–brain barrier [18-20]. Recently, Schmidt et al showed that BDNF administered subcutaneously using an implanted osmotic mini-pump produced antidepressant-like responses in mouse brain cells, and resulted in antidepressant-like behaviors in mice [21]. Schmidt et al showed that BDNF levels were elevated in the hippocampus of adult mice, and that hippocampal neurogenesis was increased after chronic, peripheral BDNF administration [21]. These findings suggest that increased peripheral BDNF affects hippocampal BDNF levels and neurogenesis, causing antidepressant effects.

In addition, mental stress is a common precipitating factor for MDD, and can also cause endothelial dysfunction, which has been shown to be an early risk factor for the development of severe cardiovascular disorders [22]. Broadley et al demonstrated that acute stress resulted in increased cortisol levels and endothelial dysfunction, and showed that such responses were prevented by inhibition of cortisol production with metyrapone [23]. In a recent clinical study, Chumaeva et al concluded that chronic stress impairs vascular-endothelium functions, and increases the development of early atherosclerosis [24].

This evidence shows that stress can cause vascular endothelial dysfunction, resulting in decreased BDNF production in the vascular endothelium and reduced blood levels of BDNF. The reduced blood levels of BDNF may affect brain BDNF levels, contributing to major depression. Decreased BDNF production by cerebrovascular endothelial cells may also have a direct impact on brain BDNF levels.

This hypothesis is further supported by antidepressant medications and exercise being able to improve vascular endothelial function. For example, such treatments in depressed patients with coronary artery disease showed that the endothelium-protective properties of antidepressants may result from increased levels of nitric oxide [25, 26]. Exercise training is an effective therapy targeting endothelial dysfunction, and several mechanisms have been proposed to explain the positive effects of exercise,

including a decrease in cytokine production in adipose tissue, skeletal muscle, endothelium, and blood mononuclear cells, as well as increases in the bioavailability of nitric oxide, antioxidant defenses, and the regenerative capacity of the endothelium [27]. Thus, antidepressant treatments [12, 13] and exercise [28, 29] may increase the blood levels of BDNF through endothelium-protective effects.

Tests for the Hypothesis

The above evidence suggests that the low serum BDNF levels in MDD patients could be the result of reduced BDNF synthesis in vascular endothelial cells that may contribute to MDD pathogenesis. This hypothesis could be tested in patients with major depression. For example, endothelial dysfunction can be detected using simple and non-interventional methods. Flow-mediated dilation method (FMD; endothelial-dependent vasodilation), which can be carried out noninvasively with ultrasonography on the brachial artery, is a frequently used method for the assessment of endothelial dysfunction [30]. With this method, it would be of interest to compare the endothelial function in subjects with depression and normal controls. Furthermore, testing whether the severity of the endothelial dysfunction may affect serum BDNF levels and depression severity in depressed patients can provide evidences to disprove or disprove this hypothesis.

The etiology of MDD is unclear. However, it is likely that individual cases may result from a number of heterogeneous factors. Decreased vascular-endothelial BDNF production may be a primary contributor to the pathogenesis of MDD, especially with comorbid cardiovascular disease. Further investigation of the associations between decreased vascular endothelial BDNF production and MDD pathogenesis may lead to new, potentially important insights into MDD pathogenesis, and may also contribute to the development of novel strategies for the prevention and management of this common mental disorder.

References

[1] Duman, R. S., Heninger, G. R., Nestler, E. J. A molecular and cellular theory of depression. *Archives of General Psychiatry* (1997), 54(7), 597-606.

[2] Duman, R. S. Synaptic plasticity and mood disorders. *Molecular Psychiatry* (2002) 7 (Suppl 1), S29-S34.

[3] Smith, M. A., Makino, S., Kvetnansky, R., Post, R. M. Stress and glucocorticoids affect the expression of brain-derived neurotrophic factor and neurotrophin-3 mRNAs in the hippocampus. *The Journal of Neuroscience* (1995), 15(3 Pt 1), 1768-1777.

[4] Roceri, M., Hendriks, W., Racagni, G., Ellenbroek, B. A., Riva, M. A. Early maternal deprivation reduces the expression of BDNF and NMDA receptor subunits in rat hippocampus. *Molecular Psychiatry* (2002), 7(6), 609-616.

[5] Siuciak, J. A, Lewis, D. R, Wiegand, S. J, Lindsay, R. M. Antidepressant-like effect of brain-derived neurotrophic factor (BDNF). *Pharmacology Biochemistry and Behavior* (1997), 56(1), 131-137.

[6] Luo, K. R, Hong, C. J, Liou, Y. J, Hou, S. J, Huang, Y. H, Tsai, S. J. Differential regulation of neurotrophin S100B and BDNF in two rat models of depression. *Progress in Neuro-Psychopharmacology & Biological Psychiatry* (2010), 34(8), 1433-1439.

[7] Fumagalli, F., Calabrese, F., Luoni, A., Shahid, M., Racagni, G., Riva, M. A. The AMPA receptor potentiator Org 26576 modulates stress-induced transcription of BDNF isoforms in rat hippocampus. *Pharmacological Research* (2012), 65(2), 176-181.

[8] Chen, B., Dowlatshahi, D., MacQueen, G.M., Wang, J.F., Young, L.T. Increased hippocampal BDNF immunoreactivity in subjects treated with antidepressant medication. Biological Psychiatry (2001), 50(4), 260-265.

[9] Dunham, J. S., Deakin, J. F., Miyajima, F., Payton, A., Toro, C. T. Expression of hippocampal brain-derived neurotrophic factor and its receptors in Stanley consortium brains. *Journal of Psychiatric Research* (2009), 43 (14), 1175-1184.

[10] Kozicz, T., Tilburg-Ouwens, D., Faludi, G., Palkovits, M., Roubos, E. Gender-related urocortin 1 and brain-derived neurotrophic factor expression in the adult human midbrain of suicide victims with major depression. *Neuroscience* (2008), 152(4), 1015-1023.

[11] Karege, F., Perret, G., Bondolfi, G., Schwald, M., Bertschy, G., Aubry, J. M. Decreased serum brain-derived neurotrophic factor levels in major depressed patients. *Psychiatry Research* (2002), 109(2), 143-148.

[12] Shimizu, E., Hashimoto, K., Okamura, N., Koike, K., Komatsu, N., Kumakiri, C., et al. Alterations of serum levels of brain-derived neurotrophic factor (BDNF) in depressed patients with or without antidepressants. *Biological Psychiatry* (2003), 54(1), 70-75.

[13] Sen, S., Duman, R., Sanacora, G. Serum brain-derived neurotrophic factor, depression, and antidepressant medications: meta-analyses and implications. *Biological Psychiatry* (2008), 64(6), 527-532.

[14] Radka, S. F., Holst, P. A., Fritsche, M., Altar, C. A. Presence of brain-derived neurotrophic factor in brain and human and rat but not mouse serum detected by a sensitive and specific immunoassay. *Brain Research* (1996), 709(1), 122-130.

[15] Fujimura, H., Altar, C. A., Chen, R., Nakamura, T., Nakahashi, T., Kambayashi, J. I., et al. Brain-derived neurotrophic factor is stored in human platelets and released by agonist stimulation. *Thrombosis and Haemostasis* (2002), 87(4), 728-734.

[16] Nakahashi, T., Fujimura, H., Altar, C. A., Li, J., Kambayashi, J., Tandon, N. N., et al Vascular endothelial

cells synthesize and secrete brain-derived neurotrophic factor. *FEBS Letters* (2000), 470(2), 113-117.

[17] Bayas, A., Hummel, V., Kallmann, B.A., Karch, C., Toyka, K. V., Rieckmann, P. Human cerebral endothelial cells are a potential source for bioactive BDNF. *Cytokine* (2002), 19(2), 55-58.

[18] Pan, W., Banks, W. A., Fasold, M. B., Bluth, J., Kastin, A. J. Transport of brain-derived neurotrophic factor across the blood-brain barrier. *Neuropharmacology* (1998), 37(12), 1553-1561.

[19] Zhang, Y., Pardridge, W. M. Blood-brain barrier targeting of BDNF improves motor function in rats with middle cerebral artery occlusion. *Brain Research* (2006), 1111(1), 227-229.

[20] Poduslo, J. F., Curran, G. L. Permeability at the blood-brain and blood-nerve barriers of the neurotrophic factors: NGF, CNTF, NT-3, BDNF. *Brain Research Molecular Brain Research* (1996), 36(2), 280-286.

[21] Schmidt, H. D., Duman, R. S. Peripheral BDNF produces antidepressant-like effects in cellular and behavioral models. *Neuropsychopharmacology* (2010), 35(12), 2378-2391.

[22] Toda, N., Nakanishi-Toda, M. How mental stress affects endothelial function. *Pflügers Archiv : EuropeanJjournal of Physiology* (2011), 462(6), 779-794.

[23] Broadley, A. J., Korszun, A., Abdelaal, E., Moskvina, V., Jones, C. J., Nash, G. B., et al Inhibition of cortisol production with metyrapone prevents mental stress-induced endothelial dysfunction and baroreflex impairment. *Journal of the American College of Cardiology* (2005), 46(2), 344-350.

[24] Chumaeva, N., Hintsanen, M., Juonala, M., Raitakari, O. T., Keltikangas-Järvinen, L. Sex differences in the combined effect of chronic stress with impaired vascular endothelium functioning and the development of early atherosclerosis: the Cardiovascular Risk in Young Finns study. *BMC Cardiovascular Disorder* (2010), 10, 34.

[25] Serebruany, V. L., Glassman, A. H., Malinin, A. I., Nemeroff, C. B., Musselman, D. L., van Zyl, L. T., et al. Platelet/endothelial biomarkers in depressed patients treated with the selective serotonin reuptake inhibitor sertraline after acute coronary events: the Sertraline AntiDepressant Heart Attack Randomized Trial (SADHART) Platelet Substudy. *Circulation* (2003), 108(8), 939-944.

[26] van Zyl, L. T., Lespérance, F., Frasure-Smith, N., Malinin, A. I., Atar, D., Laliberté, M. A, et al. Platelet and endothelial activity in comorbid major depression and coronary artery disease patients treated with citalopram: the Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy Trial (CREATE) biomarker sub-study. *Journal of Thrombosis and Thrombolysis* (2009), 27(1), 48-56.

[27] Ribeiro, F., Alves, A. J., Duarte, J. A., Oliveira, J. Is exercise training an effective therapy targeting endothelial dysfunction and vascular wall inflammation? *International Journal of Cardiology* (2010), 141(3), 214-221.

[28] Tang, S. W., Chu, E., Hui, T., Helmeste, D., Law, C. Influence of exercise on serum brain-derived neurotrophic factor concentrations in healthy human subjects. *Neuroscience Letters* (2008), 431(1), 62-65.

[29] Swardfager, W., Herrmann, N., Marzolini, S., Saleem, M., Shammi, P., Oh, P. I., et al. Brain derived neurotrophic factor, cardiopulmonary fitness and cognition in patients with coronary artery disease. *Brain, Behavior, and Immunity* (2011), 25(6), 1264-1271.

[30] Korkmaz, H., Onalan, O. Evaluation of endothelial dysfunction: flow-mediated dilation. *Endothelium* (2008), 15(4), 157-163.